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Diabetes Insipidus: New Concepts for Diagnosis

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Abstract
Diabetes insipidus (DI), be it from central or from nephrogenic origin, has to be differentiated from primary polydipsia. This differentiation is crucial since wrong treatment can have dangerous consequences. For decades, the "gold standard" for differential diagnosis has been the standard water deprivation test. However, this test has several limitations leading to an overall limited diagnostic accuracy. In addition, the test has a long duration of 17 h and is cumbersome for patients. Also clinical signs and symptoms and MRI characteristics overlap between patients with DI and primary polydipsia. Direct measurement of arginine vasopressin (AVP) upon osmotic stimulation was first shown to overcome these limitations, but failed to enter clinical practice mainly due to technical limitations of the AVP assay. Copeptin is secreted in equimolar ratio to AVP, mirroring AVP concentrations in the circulation. We have shown that copeptin, without prior fluid deprivation, identifies patients with nephrogenic DI. For the more difficult differentiation between central DI and primary polydipsia, a copeptin level of 4.9 pmol/L stimulated with hypertonic saline infusion differentiates between these 2 entities with a high diagnostic accuracy and is superior to the water deprivation test. However, it is important to note that close and regular sodium monitoring every 30 min during the hypertonic saline test is a prerequisite, which is not possible in all hospitals. Furthermore, side effects are common. Therefore, a nonosmotic stimulation test would be advantageous. Arginine significantly stimulates copeptin and therefore is a novel, so far unknown stimulus of this peptide. Consequently, infusion of arginine with subsequent copeptin measurement was shown to be an even simpler and better tolerated test, but head to head comparison is still lacking.

Introduction

Diabetes insipidus (DI) is part of the so-called polyuria polydipsia syndrome. This syndrome is defined by an output of >50 mL/kg body weight per 24 h of hypotonic urine (<300 mOsm/kg H_2O), which is accompanied by polydipsia of >3 L a day [1]. The differential diagnosis of hypotonic polyuria includes central or nephrogenic DI on 1 hand and primary polydipsia on the other hand. A correct differential diagnosis is important since treatment differs and application of the wrong treatment may lead to deleterious clinical consequences for the patients, such as water intoxication if treatment with Desmopressin is applied to patients with primary polydipsia.

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The "gold standard" for differential diagnosis for decades has been the classical, standard water deprivation test. This test, however, has several limitations leading to a rather low diagnostic accuracy of only around 70%. Therefore, Zerbe and Robertson [2] proposed in the 1980s to directly measure arginine vasopressin (AVP) upon osmotic stimulation with hypertonic saline. Initial results looked promising, but unfortunately, measurement of AVP did not enter clinical practice, mainly due to technical limitations of the AVP assay and due to the fact that reliable assays are mostly not commercially available. In this review, we will therefore discuss new concepts for the diagnosis and differential diagnosis of the polyuria polydipsia syndrome.

The Polyuria Polydipsia Syndrome

The polyuria polydipsia syndrome includes central or nephrogenic DI on 1 hand and primary polydipsia on the other hand [3]. It is not uncommon in clinical practice with increasing prevalence especially since many lifestyle programs suggest that consuming several liters of fluids a day is generally healthy.

DI leads to hypotonic polyuria which is usually accompanied by subsequent polydipsia. In central DI, there is an insufficient secretion of AVP from the posterior pituitary [4, 5]. Central DI is most often induced by lesions of the posterior pituitary or the hypothalamic median eminence. The most common acquired causes are trauma, surgery of the pituitary, neoplastic, vascular, autoimmune, infectious, or granulomatous diseases. Pituitary surgery leads to central DI in up to 30% of cases, which is most often of transient nature. Permanent postsurgical DI is much less common and only occurs in 2–10% [6]. Central DI can also be inherited, however, inherited forms are rather rare [7, 8]. As mentioned above, in most cases, thirst mechanisms are intact, therefore leading to a subsequent polydipsia. If thirst mechanisms are also impaired, as happens in the so-called osmoreceptor dysfunction, lack of polydipsia may lead to hyperosmolality and dehydration which can have clinically serious complications [3, 9].

In contrast, in nephrogenic DI, AVP levels are normally secreted, but there is a resistance toward the action of AVP at the level of the kidneys [10]. Nephrogenic DI is also most often acquired, with the best known cause being drug-induced nephrogenic DI. Mainly lithium intake is known to induce nephrogenic DI [10]. Furthermore, it can also be inherited, with mutations the key proteins of AVP receptor 2 and aquaporin 2.

In primary polydipsia, AVP secretion and renal action are not affected. The primary problem is an excessive fluid intake over a longer period of time. Very rarely, it can result from an abnormality in the thirst center (in which case it is called dipsogenic DI). However, much more often, it is seen in different psychiatric disorders (called psychogenic polydipsia). Subsequent to the excessive fluid intake osmolality and AVP synthesis and release are suppressed. The consequence is excretion of free water. If polydipsia is happening over an extended period of time, it can result in reno-physiological adaptions, including first a downregulation of the aquaporin 2 channels in the kidneys and second compromising the renal medullary concentration gradient. Both these processes are factors limiting urinary concentration capacity. Clear diagnostic distinction between the different forms of DI and primary polydipsia is critical as causal treatment obviously varies and application of the wrong treatment can be clinically harmful and potentially life-threatening [11].

Differential Diagnosis by Water Deprivation Test

For many years, the standard diagnostic test for the evaluation of polyuria-polydipsia syndrome was the classical water deprivation test [5]. With this test, insufficient AVP secretion or effect is diagnosed upon insufficient concentration capacity of the kidneys over osmotic stimulation which is reached with a prolonged period of thirsting (usually 16 h) and its response to exogenous AVP administration (Desmopressin) [12–14]. The classical interpretation of the test is based on results on data from Miller et al. [5]. In this study, 29 patients with central DI (11 with a partial DI), 2 patients with nephrogenic DI and 5 patients with primary polydipsia were evaluated. Patients with a urinary osmolality below 300 mOsm/kg during the water deprivation test are diagnosed to have complete DI. If these patients increase with their urinary osmolality >50% after exogenous AVP administration, the final diagnosis is complete central DI, and conversely, if their urinary osmolality after exogenous AVP administration does increase <50%, the final diagnosis is complete nephrogenic DI. In those patients in whom urinary osmolalities increased to values between 300 and 800 mOsm/kg upon water deprivation, partial central DI, or primary polydipsia is present. Partial central DI patients increased upon exogenous AVP administration >9%, whereas patients with primary polydipsia increased <9%.

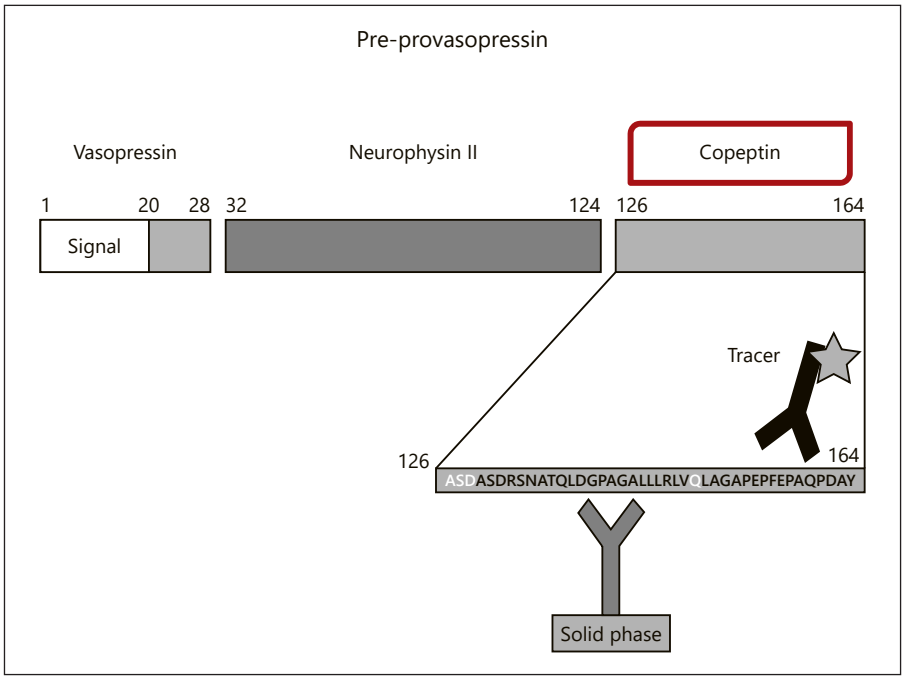

Fig. 1. AVP and its protein products. The prohormone is packaged into neurosecretory granules of magnocellular neurons. During axonal transport of the granules from the hypothalamus to the posterior pituitary, enzymatic cleavage of the prohormone generates the final products: AVP, neurophysin and the COOH-terminal glycoprotein copeptin. Adapted from [3].

However, these cutoff values derive from only one single post hoc analysis of this small cohort of patients and as evident in the raw data show a quite wide overlap in urinary osmolality levels [5]. Recent data in fact, aiming to validate these findings, showed a diagnostic accuracy of using these criteria in the classical water deprivation test of only around 70%, with an especially low diagnostic accuracy in patients with primary polydipsia [12, 14].

To improve the differential diagnosis of the polyuria polydipsia syndrome, Zerbe and Robertson [2] proposed the direct test, where plasma AVP is measured upon osmotic stimulation not only by thirsting, but by stimulation with hypertonic saline infusion. AVP-levels are then interpreted in relation to the area of normality describing the physiological relationship between AVP release and plasma osmolality. Patients with osmotically stimulated plasma AVP levels above the area of normality are diagnosed as nephrogenic DI, patients with levels below the area of normality as central DI, and patients with levels within the normal area as primary polydipsia [2, 7]. Reassuringly, the results showed that direct measurement of plasma AVP has the potential to improve the diagnostic accuracy of the classical "indirect" water deprivation test with interpretation of urinary osmolality levels. However, despite these promising data, this direct test based on AVP measurement did not enter everyday clinical routine. Unfortunately, recent studies failed to confirm these promising data when using commercially available AVP assays. Specifically, with commercially available assays, a correct diagnosis was only reached in 38% of patients and a diagnostic accuracy was especially low in the differentiation between partial central DI and primary polydipsia [12]. The problem is that an accurate definition of the normal physiological relationship describing plasma AVP as a function of osmotic activity has long been missed [15], but is an important condition for the use of direct AVP measurement [12]. Furthermore, the AVP assay per se has several technical limitations, resulting in a high preanalytical instability [1, 16, 17]. Of note, the few reliable assays are not commercially available.

Therefore, new concepts for differential diagnosis are urgently needed.

Copeptin: A New Surrogate Marker for AVP

Copeptin was originally detected in 1972 in the posterior pituitary of pigs [18, 19], and it derives from the 164 amino acid precursor protein Pre-Pro-Vasopressin together with AVP and Neurophysin II. It is a 39 amino acid long glycosylated peptide with a leucine-rich core region [19, 20] and has a molecular mass of around 5 kDa [21] (Fig. 1).

Its physiological function until today remains largely unknown.

Copeptin strongly correlates with plasma AVP with a correlation index of $r = 0.8$ [22]. Of note, the correlation of plasma copeptin with plasma osmolality was even stronger than the correlation of AVP with plasma osmolality [23], most likely due to the complexity and methodological drawbacks of the AVP assay.

Processed from the same precursor peptide, the release of plasma copeptin and plasma AVP into circulation is regulated by the same physiological stimuli, which is a relative increase in systemic osmolality and a relative decrease in arterial blood volume and pressure [22, 24]. The surrogate properties of copeptin for physiological AVP release secondary to osmotic regulation was first shown in a study including 24 healthy adults, where fluid deprivation as well as hypertonic saline infusion led to a significant increase in plasma copeptin levels [23, 24].

There are also nonosmotic stimuli for AVP and copeptin such as nausea, hypovolemia, and hypotension as well as unspecific somatic stress as seen in, for example, ischemic stroke, myocardial infarction, or pneumonia [25–27].

In contrast to AVP, copeptin can be measured in clinical routine with commercially available assays with a high-standard technical performance. Two assays are currently available and validated, on 1 side the original manual sandwich immunoluminometric assay [21] and on the other side the automated immunofluorescent successor (on the KRYPTOR platform). Main advantages of measuring copeptin as compared to AVP are that it requires only a small sample volume (50 μL of serum or plasma), no extraction step, or other preanalytical procedures, and that results are normally available in <2 h. Moreover, copeptin is much more stable in plasma or serum ex vivo with <20% loss of recovery for at least 7 days at room temperature and at 14 days at 4 °C making the handling of patient blood samples less complicated.

Based on the above, copeptin could be an attractive new surrogate marker for the diagnosis and differential diagnosis of DI.

First Concept: Baseline Copeptin to Identify Nephrogenic DI and Hypertonic Saline Infusion Plus Copeptin Measurement to Diagnose DI

Based on the fact that osmotic stimulation is the strongest and best known stimulus for AVP and copeptin release, we first studied copeptin for the differential diagnosis of the polyuria polydipsia syndrome upon osmotic stimulation. We used a combined water deprivation test followed by 3% saline infusion. With this procedure, the aim was to increase plasma sodium levels to above 147 mmol/L which is only rarely reached by water deprivation alone, especially in patients with primary polydipsia or mild forms of DI. In 55 patients with nephrogenic or central DI or primary polydipsia [13], the first finding was that in patients with nephrogenic DI a single baseline copeptin level of >21.4 pmol/L without prior thirsting identified all patients with nephrogenic diabetes.

As expected, however, baseline copeptin values in all other diagnoses (i.e., central DI and primary polydipsia) largely overlapped. The second finding was that upon osmotic stimulation, a copeptin level of >4.9 pmol/L differentiated patients with central DI from patients with primary polydipsia with a high diagnostic accuracy of 96%. AVP was also measured in this study, with a validated assay, showing a slightly lower diagnostic accuracy [13].

We then validated this copeptin cutoff of 4.9 pmol/L in an international multicenter study including 156 patients with the polyuria polydipsia syndrome [14]. We further aimed to simplify the test protocol by omitting the thirsting period and by using only the hypertonic saline infusion, with the aim to increase plasma sodium levels to at least 150 mmol/L. Toward this aim, hypertonic saline was initially given as a bolus dose, followed by a continuous infusion rate of 0.15 mL/kg/min until the serum sodium concentration exceeded ≥150 mmol/L. At this time point, copeptin was measured, and serum osmolality was normalized by glucose infusion and standardized fluid intake [14]. The results showed that 97% of the patients were correctly diagnosed with the predefined copeptin cutoff level of >4.9 pmol/L (Fig. 2). The diagnostic accuracy was similar in the differential diagnosis of patients with partial DI and patients with primary polydipsia with a correct diagnosis in 95%.

The high diagnostic accuracy is reassuring – however, it is important to note that hypertonic saline infusion requires close and regular monitoring of sodium levels every 30 min to ensure increase of plasma sodium levels into the hyperosmotic range [4, 28] while preventing osmotic overstimulation [14]. Also rapid normalization of sodium levels after the osmotic stimulation is crucial to guarantee the safety of the test [14].

Based on these results, it was concluded that the hypertonic saline test plus copeptin measurement might replace the classical water deprivation test in the future differential diagnosis of hypotonic polyuria [29].

Side effects such as headache, vertigo, and malaise were more common during the hypertonic saline infusion test

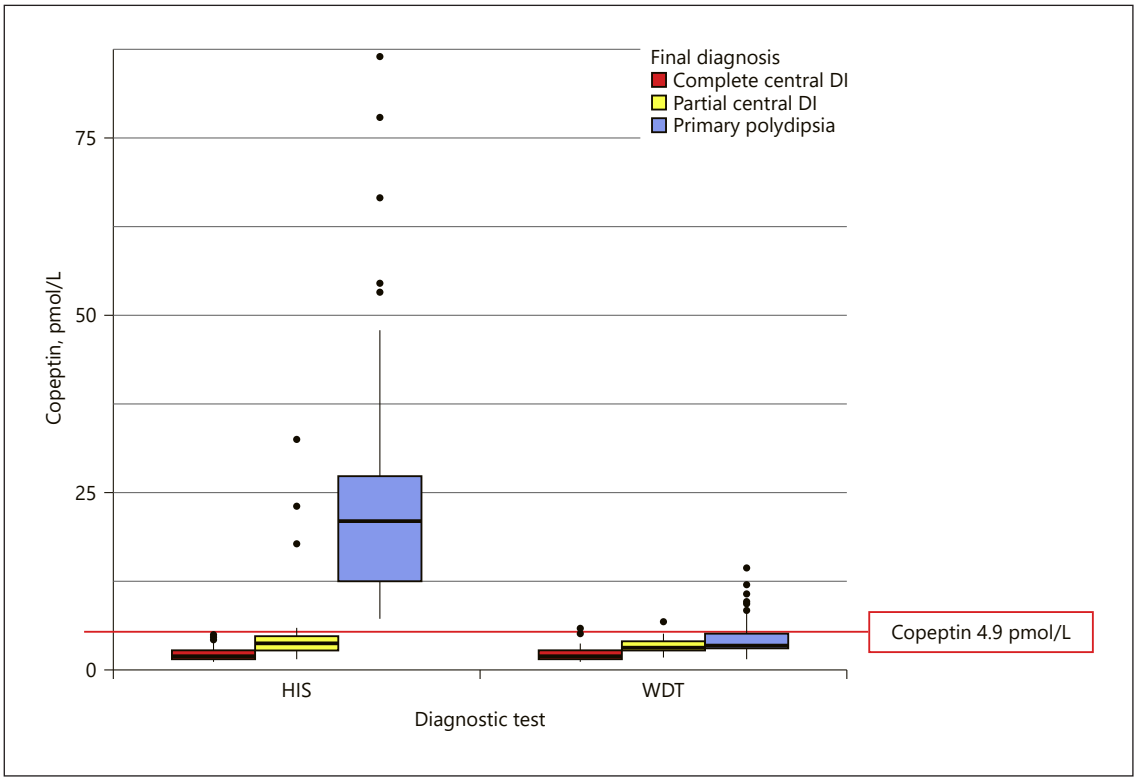

Fig. 2. Copeptin after hypertonic saline infusions compared to the classical water deprivation test in patients with complete or partial central DI or primary polydipsia [14]. DI, diabetes insipidus; HIS, hypertonic infusion of saline; WDT, water deprivation test.

than with the classical water deprivation test. Still, the majority of patients preferred the hypertonic saline stimulation with copeptin measurement over the standard water deprivation test. Most probably, the reason was the clearly shorter test duration (approximately 2 h for the hypertonic saline test versus 17 h for the water deprivation test) [14].

However, although these results are very reassuring in terms of diagnostic accuracy, the hypertonic saline infusion test is based on the induction of hypernatremia and has, therefore, several caveats, as just mentioned above: the rise in sodium can be associated with adverse effects and the test requires therefore close monitoring of sodium levels.

Therefore, a nonosmotic stimulus without the need to induce hyperosmolality would be more favorable.

Second Concept: Nonosmotic Stimulation with Arginine Plus Copeptin Measurement to Diagnose DI

Arginine is known to stimulate various hormones secreted by the anterior pituitary gland such as prolactin [30, 31] and growth hormone [32]. Arginine stimulation is, therefore, widely used as a simple and well-tolerated tool to diagnose growth hormone deficiency [33, 34], especially in children [35].

In accordance with the effects of other growth hormone secretagogues (e.g., hexarelin) [36, 37], we therefore hypothesized that arginine would also stimulate the posterior pituitary (vasopressin/copeptin) and might therefore provide a simple and alternative diagnostic test in the differential diagnosis of DI. We first showed that arginine indeed is a novel nonosmotic stimulus in healthy adults and children: in healthy adults, median (interquartile range) baseline copeptin levels were 5.2 pmol/L (3.3–10.9) and increased within the first 60 min after arginine stimulation to 9.8 pmol/L (6.4–19.6; $p < 0.001$) and plateaued thereafter. In children, copeptin levels increased from baseline 4.3 pmol/L (3.2–6.0) to 6.5 pmol/L (4.7–8.5; $p < 0.001$) within the first 60 min after arginine stimulation and decreased thereafter.

In patients with polyuria polydipsia syndrome, the highest diagnostic accuracy for differentiating between DI and primary polydipsia was observed for a copeptin cutoff of 3.8 pmol/L, measured at 60 min after arginine stimulation, 93%

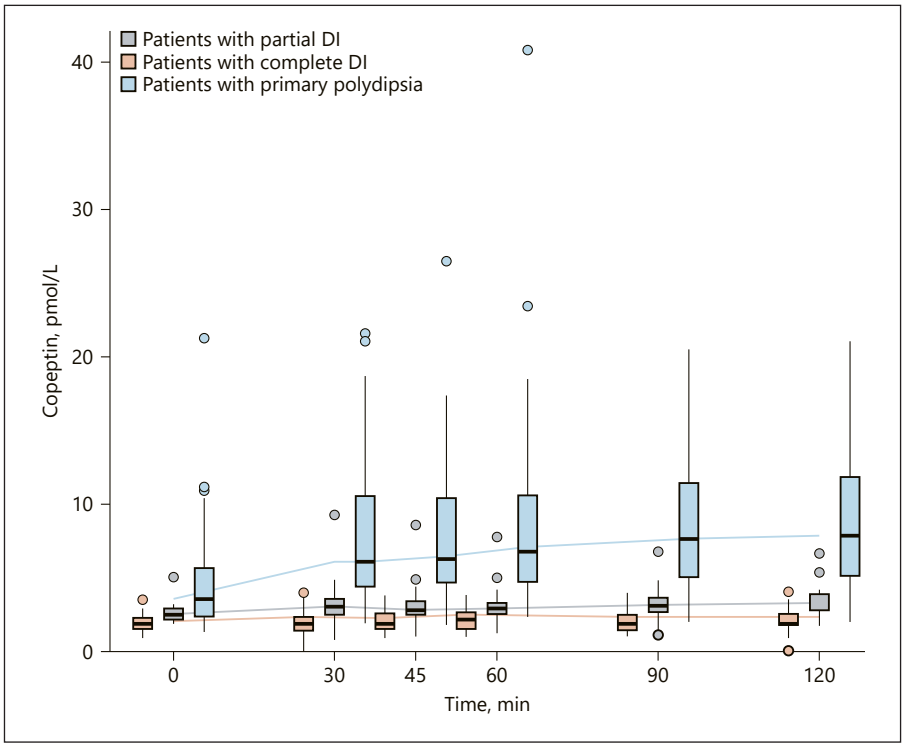

Fig. 3. Copeptin after arginine infusion, in patients with complete or partial central DI and in primary polydipsia. Adapted from [40]. DI, diabetes insipidus.

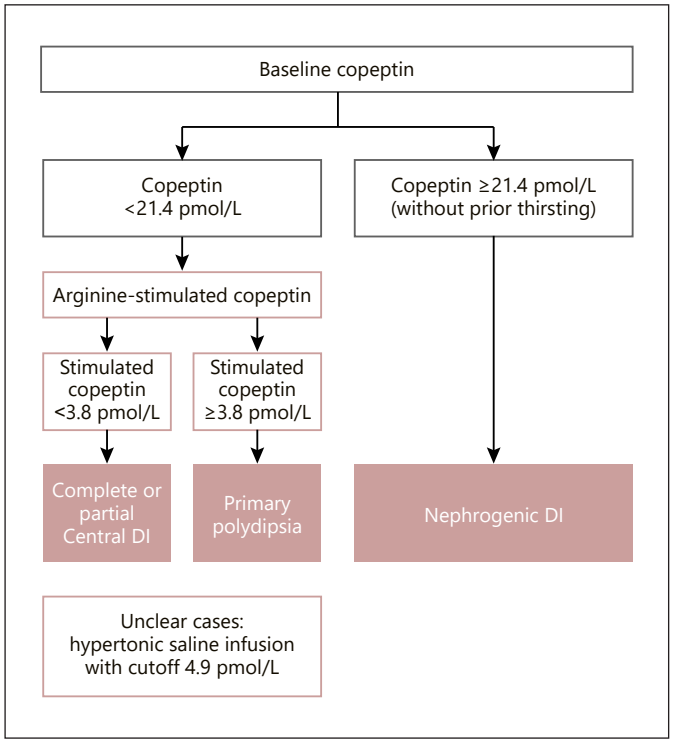

Fig. 4. Proposed two-step algorithm for the differential diagnosis of polyuria polydipsia syndrome. DI, diabetes insipidus.

(95% CI 86–97), with a sensitivity of 93% and a specificity of 92%. The area under the curve for the corresponding receiver operating characteristic was 0.95 (95% CI 0.92–0.99). Likewise, the highest diagnostic accuracy for differentiating between partial DI and primary polydipsia was found for a copeptin cutoff of 3.8 pmol/L, measured at 60 min after arginine stimulation, 90% (95% CI 82–96), with a sensitivity of 93% and a specificity of 80%. The area under the curve for the corresponding receiver operating characteristic was 0.91 (95% CI 0.83–0.99; Fig. 3).

During arginine stimulation, clinical and laboratory parameters remained generally stable and within the normal range. Overall, the test burden was rated to be low, although nausea was a frequent symptom during arginine stimulation. Compared to hypertonic saline stimulation, which is associated with adverse effects in the majority of patients [14], the tolerability profile of arginine stimulation is clearly more attractive.

However, to be able to draw inference about the comparative performance of both tests, a prospective head-to-head evaluation is currently being performed.

At the moment, a step-wise approach may be recommended, with the easier arginine stimulation test as first test and the hypertonic saline infusion test in unclear cases as the second test. A respective algorithm is proposed in Figure 4.

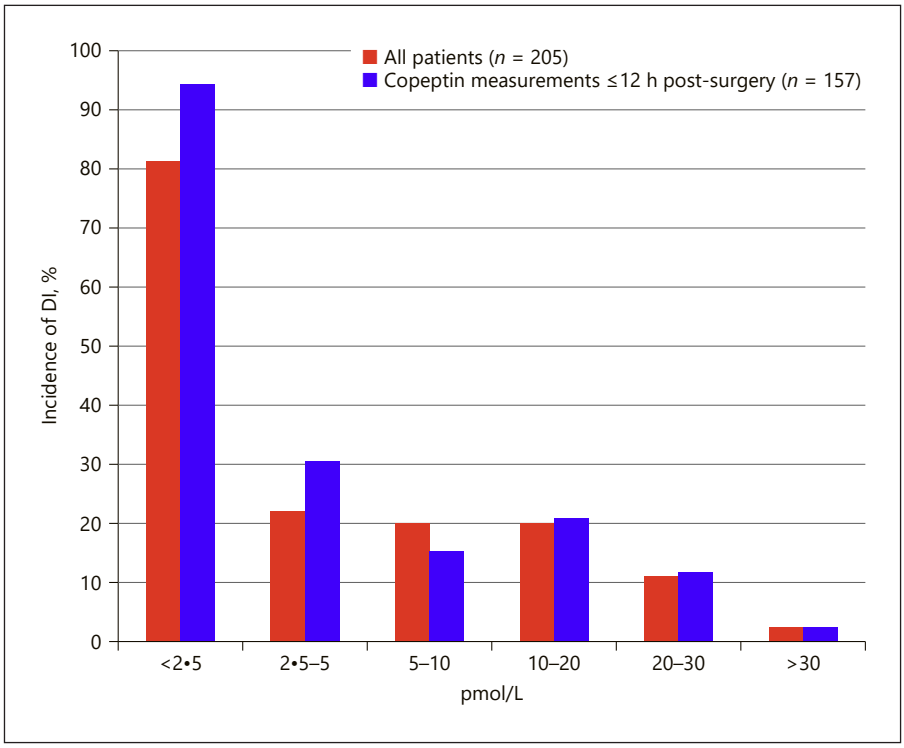

Fig. 5. Copeptin in the diagnosis of post-surgical DI. DI, diabetes insipidus.

Third Concept: Nonosmotic Stress-Induced Copeptin to Diagnose Postsurgical DI

In a proof-of-concept study in 2007, it was shown that in patients after pituitary surgery, an insulin tolerance test inducing hypoglycemia and therefore a nonosmotic stress led to a significant induction of copeptin levels in those patients with an intact posterior pituitary function, but copeptin levels remained low in patients with postsurgical DI [38]. Copeptin levels of patients with intact posterior pituitary showed a maximal increase to 11.1 ± 4.6 pmol/L, while copeptin levels in patients with central DI remained low upon hypoglycemia at 3.7 ± 0.7 pmol/L. A hypoglycemic stimulated copeptin level <4.75 pmol/L had an optimal diagnostic accuracy to detect central DI of 100%.

Clearly, however, induction of hypoglycemia is not an attractive test for differential diagnosis of polyuria polydipsia syndrome and is not feasible as a routine test since it can be associated with severe hypoglycemia and is contraindicated in patients with cardiovascular disease or seizure history and despite its reliable diagnostic performance, the insulin tolerance test is also not appropriate in the immediate postoperative recovery phase.

However, surgery – itself known as a stressful event stimulating hypothalamic stress hormone release including AVP [39], – can be used as a "stress test" to assess functionality of AVP and copeptin secretion. In a prospective multicenter trial including 205 patients undergoing pituitary surgery, 24% of patients developed postoperative central DI. Those patients had significantly lower copeptin levels on the first postoperative day compared to patients without postoperative DI. The post hoc derived copeptin cutoff level of <2.5 pmol/L had a positive predictive value for development of central DI of 81% and a specificity of 97%, while a level >30 pmol/L excluded it with a negative predictive value of 95% and a sensitivity of 94% (Fig. 5). Accordingly, copeptin measurement after pituitary surgery is helpful to predict the onset of central DI, allowing earlier targeted therapeutic measures. Even though measurement of urine volume and osmolality can identify patients with postoperative DI in most cases, these findings have implications especially in view of the nowadays often early discharge of patients after pituitary surgery. Based on our findings, copeptin measurement in patients with pituitary surgery may identify patients benefitting from closer inpatient observation and patients in whom early hospital discharge is safely possible. Of note, copeptin is only helpful for risk stratification if the value is either very low (<2.5 pmol/L) or very high (>30 pmol/L).

Conclusions

In conclusion, the diagnosis and differential diagnosis of DI has long been made by the cumbersome water deprivation test, which has a limited diagnostic accuracy. The direct test using hypertonic saline infusion plus AVP measurement did not enter clinical routine mainly due to technical limitations of the AVP assay. Copeptin is a stable surrogate marker of AVP and provides a valuable and reliable diagnostic marker in the differential diagnosis of the polyuria-polydipsia syndrome. In patients with hypotonic polyuria, measurement of basal copeptin levels identifies nephrogenic DI. In all other patients, copeptin measurement after osmotic stimulation with 3% saline solution with the aim to increase plasma sodium level ≥150 mmol/L is recommended. Importantly, close monitoring of plasma sodium levels [14]. An even simpler and better tolerated alternative without the need to induce hypernatremia is the arginine stimulation test. In patients after pituitary surgery, a stress-induced high copeptin level immediately after surgery merely excludes later DI, whereas a low levels is highly predicting for later DI.

Disclosure Statement

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